Early Exposure to Bacterial and Microbial Products Decreases Risk of Asthma

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General Information	
Broad Focus Area	Asthma
Background and Justification	Starting in the late 1980's a number of papers suggested that "…allergic diseases were prevented by infection in early childhood…" This hypothesis ran counter to observations that infection is generally an allergenic stimulus.[1] Initial investigations focused on epidemiologic associations between family size, birth order, and attendance in daycare on the risk of asthma and other allergic disorders. Subsequent investigation has examined immunologic profiles of people with and without asthma, as well as patterns of early infection and exposure to bacterial endotoxin among children with and without asthma.[2] General findings from these studies can be interpreted to suggest that asthma is associated with a failure of the immune system to develop normally. This lack of immunologic maturity may be associated with decreased early life exposure to certain infections (e.g., M. tuberculosis, measles, Hepatitis A) or microbial products in general (e.g., bacterial endotoxin) that directly stimulate the Th-1 lymphocyte response. Attenuation of the normal change from a predominantly Th-2 lymphocyte response to stimuli, associated with allergic inflammation, to a balanced response between Th-1 (associated with cellular defense) and Th-2 lymphocytes has been postulated as a potential mechanism for increased asthma risk.[3, 4] The degree to which asthma etiology can be directly related to decreased exposure to certain infections or microbial products; the necessary timing of these exposures to initiate optimal immune response throughout life (or, whether the immunologic response is programmed in utero[5]); and individual variation in response to early infections are in need of additional in-depth investigation to further development of asthma prevention and treatment strategies.
Prevalence/ Incidence	Nine million children under 18 years of age are estimated to have asthma.[6] Among children, it is the most common chronic illness.[7] The prevalence of asthma increased from 35 to 62 per 1,000 children aged 0 to 17 years between 1980 and 1996.[8]
Economic Impact	In 1997, the annual estimated cost of pediatric asthma in the US was $6.6 billion.[9] By 2002, the total cost of asthma was estimated at $14 billion.[10] The more severe forms of asthma account for a disproportionate amount of the total direct costs; one study estimated that less than 20% of asthmatics account for over 80% of the direct costs.[11] Asthma also poses a substantial and increasing public health burden in lost time from school and usual activities and in health care utilization.

Exposure Measures			Outcome Measures	
Primary/ Maternal	Prenatal exposure to bacteria and microbial products		***Primary/ Maternal***	
Methods	Medical record review; interview/questionnaire; blood samples; urine samples; other physical sampling		Methods	

Life Stage	Prenatal through birth		Life Stage	
Primary/Child	Exposure to bacteria and microbial products via air survey and other infection measures		***Primary/Child***	Decreased risk of asthma measured via allergy, asthma in index child, airway reactivity
Methods	Household environmental sampling; blood samples; urine samples; other physical sampling; interview/questionnaire (to assess diet, daycare attendance, exposure to pets, etc.); medical record review		Methods	Direct observation by medical professional; medical record review; interview/questionnaire; blood samples; urine samples; other physical sampling
Life Stage	Repeated, birth through year 5		Life Stage	Repeated, birth to year 20

Important Confounders/Covariates	
Infection history	Site, type of prior infection, e.g., respiratory, gastrointestinal does not change likelihood of protective effect [12, 13]
Medication use	Antibiotic and/or paracetamol use may increase the risk of asthma [12]
Living conditions	Living in uncrowded conditions and in higher SES conditions reduces risk of asthma [14]

Population of Interest		**Estimated Effect that is Detectable**
All children		The smallest detectable relative risk is approximately 1.2. This power estimate assumes a sample size of 100,000 at age of diagnosis, an asthma incidence of 5%, and a cut-off value for "high" exposure based on the upper 5th percentile of NCS subjects (i.e., a proportion exposed of 0.05). It assumes only a main effects model based on exposure to a single factor (e.g., early exposure to bacterial and microbial products) without consideration of interactions with other exposures, genetics, family history, etc.[15]

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